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EFFECTS OF EXPOSURE TO HEAVY PARTICLES ON A BEHAVIOR MEDIATED BY THE DOPAMINERGIC SYSTEM

B.M. Rabin[1], J.A. Joseph[2], B. Shukitt-Hale[2], and J. McEwen[2]

[1]*Dept. of Psychology, University of Maryland Baltimore County, Baltimore, MD, 21250 U.S.A.*
[2]*Human Nutrition Research Center on Aging, USDA-ARS, Tufts Univ., Boston, MA, 02111 U.S.A.*

ABSTRACT

The effects of exposure to heavy particles on behaviors mediated by the central nervous system (CNS) are qualitatively different than the effects produced by exposure to other types of radiation. One behavior mediated by the CNS is the amphetamine-induced taste aversion, which is produced by pairing a novel tasting solution with injection of amphetamine. When the conditioning day is three days following irradiation, exposing rats to low doses of ^{56}Fe particles (600 MeV/n or 1 GeV/n) eliminates the taste aversion produced by injection of amphetamine, which is dependent upon the integrity of the central dopaminergic system, but has no effect on the aversion produced by injection of lithium chloride which is mediated by the gastrointestinal system. In contrast to the effects obtained using heavy particles, exposing rats to ^{60}Co gamma rays or to fission spectrum neutrons has no selective effect upon the acquisition of either amphetamine- or lithium chloride-induced taste aversions. When the conditioning day occurs four months following exposure to 1 GeV/n ^{56}Fe particles, there is an enhancement of the amphetamine-induced taste aversion. The implications of these findings for approaches to risk assessment are considered.

INTRODUCTION

Previous research has shown that exposing rats to low doses (≈ 0.1 Gy) of ^{56}Fe particles (600 MeV/n) produces deficits in the dopaminergic system and in the motor behavior that depends upon the integrity of that system (Hunt *et al.* 1989, 1990; Joseph *et al.*, 1992, 1993). In addition to its role in motor behavior, dopamine is also involved in the regulation of a variety of other behaviors (Hunt *et al.* 1989; Rabin *et al.*, 1994). One of these behaviors is the conditioned taste aversion (CTA) produced by the administration of the dopamine agonist amphetamine (Rabin and Hunt, 1989; Hunt and Amit, 1987). A CTA is produced when a novel tasting solution (*e.g.*, 10% sucrose solution) is paired with an unconditioned stimulus, such that the organism will avoid ingestion of that solution at a subsequent presentation (Rabin and Hunt, 1986; Riley & Tuck, 1985).

Taste aversions can be produced by treatment with both toxic (*e.g.*, lithium chloride [LiCl] or ionizing radiation) stimuli and with self-administered compounds (*e.g.*, amphetamine) (Rabin and Hunt, 1989; Hunt and Amit, 1987) . The CTA produced by either injection of LiCl or exposure to ionizing radiation results from the effects of the toxin on the peripheral nervous system and is dependent upon the integrity of the area postrema, the chemoreceptive trigger zone for emesis (Borison, 1974; Rabin *et al.*, 1983; Rabin *et al.*, 1989; Smith, 1980). In contrast, amphetamine-induced CTA learning is not disrupted by lesions of the area postrema (Rabin *et al.*, 1987); but rather, results from the effects of the compound on the central nervous system and is dependent upon the integrity of the central dopaminergic system (Rabin and Hunt, 1986, 1989).

It has been previously reported (Rabin *et al.*, 1998) that exposing rats to low doses (0.1 Gy) of 600 MeV/n ^{56}Fe particles

disrupted the acquisition of an amphetamine-induced CTA when conditioning occurred three days following irradiation, but had no effect on the acquisition of a CTA produced by injection of LiCl. In contrast, exposing the rats to fission spectrum neutrons (n^0) or ^{60}Co γ rays did not produce a similar selective disruption of the dopamine-mediated CTA. The present report presents a further characterization of that response by comparing the effects of exposure to 1 GeV/n ^{56}Fe particles with the effects of exposure to 600 MeV/n ^{56}Fe particles or exposure to fission neutrons or ^{60}Co γ rays. Additional groups of rats were tested 4-4.5 months following irradiation in order to evaluate the long-term consequences of exposure to heavy particles on neural functioning.

More specifically, the present experiments were designed to: (1) evaluate the relationship between LET and the relative biological effectiveness (RBE) of different types of radiation using a behavioral endpoint that is mediated by the central nervous system; (2) establish the threshold for the disruption of amphetamine-induced CTA learning following exposure to ^{56}Fe; (3) establish the dose-response relationships between exposure to ^{56}Fe particles and the disruption of the amphetamine-induced CTA; and (4) determine whether there was any recovery of function over time following exposure to 1 GeV/n ^{56}Fe particles.

METHODS

The subjects for all experiments were male Sprague-Dawley rats weighing 200-225 g at the start of the experiment. Rats were exposed to ^{60}Co γ rays and to fission spectrum neutrons using the sources at the Armed Forces Radiobiology Research Institute. Exposures to 600 MeV/n ^{56}Fe particles were achieved with the BEVALAC at Lawrence Berkeley National Laboratory. Rats were exposed to 1 GeV/n ^{56}Fe particles using the alternating gradient synchrotron at Brookhaven National Laboratory (BNL).

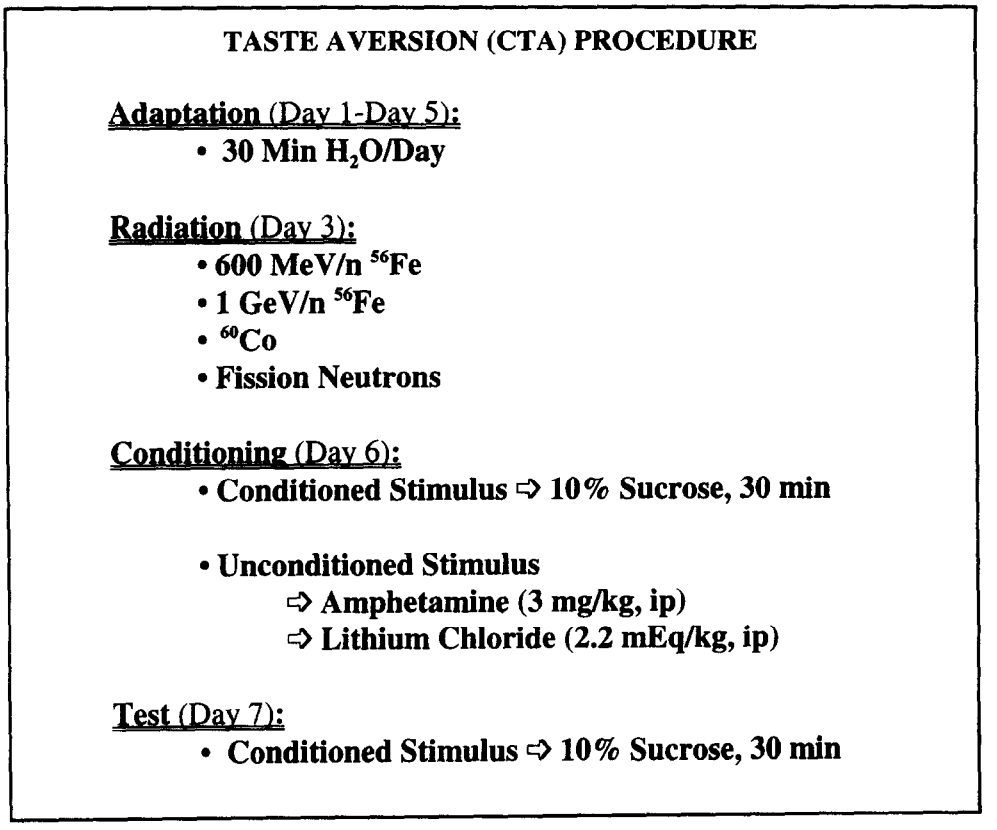

Fig. 1. Summary of the general procedure used to produce a CTA.

For exposure to heavy particles, the rats were placed in a well-ventilated plastic restraining tube which restricted the movement of the rat. The tube was placed perpendicular to the beam and positioned to provide constant exposure of the rat's head, although parts of the body were also exposed to varying lower doses of heavy particles. At energies of 600 MeV/n and 1 GeV/n, the beam of ^{56}Fe particles passed completely through the brain of the rat.

The general procedure for producing a CTA is summarized in Figure 1. Rats were first adapted to a 23.5-hr water deprivation schedule on which they received water for 30 min/day. On day 6, the water was replaced by a calibrated drinking tube containing a 10% sucrose solution and intake during the 30-min drinking period was measured. Immediately following the drinking period, the rats were administered the unconditioned stimuli, either injection of LiCl (2.2 mEq/kg, ip) or amphetamine (3 mg/kg, ip). Twenty-four hours later, the rats were again presented with the calibrated drinking tubes containing 10% sucrose for 30 min and their intake recorded. The data for all experiments are presented as test day sucrose intake as the percentage of the conditioning day sucrose intake. A CTA is shown as a reduction in test day sucrose intake compared to conditioning day intake. Statistical analysis of the data was performed using 2-way analyses of variance. Comparisons between individual groups were made utilizing procedures (protected-*t* or Scheffé procedures) to control for statistical error that might result from performing multiple *t*-tests.

The primary behavioral endpoint was the CTA produced by injection of amphetamine. The LiCl-induced CTA served as a behavioral control for possible non-specific effects produced by exposure to higher doses of radiation. The amphetamine-induced CTA was selected as the behavioral endpoint for this initial series of experiments because prior research had established that it was dependent upon the integrity of the dopaminergic system and that it could be disrupted by administration of the D_2 antagonist haloperidol (Rabin *et al.*, 1989). In addition, the task did not require sophisticated equipment or training and could therefore be utilized while working at institutions that provided access to a particle accelerator. As such, this behavior could be used to provide an initial screen to indicate whether or not exposure to low doses of heavy particles could affect other dopamine mediated behaviors in addition to upper body strength measured by wire hang-time (Hunt *et al.*, 1989; Joseph *et al.*, 1992).

As indicated in Figure 1, the conditioning day for most experiments was three days following irradiation and the test day was 24 hours later. To test for the possibility of recovery of function, 30 rats which had been exposed to 1 Gy of 1 GeV/n ^{56}Fe particles and 21 non-exposed control rats were returned to the University of Maryland Baltimore County (UMBC) from BNL. The basic procedures were as outlined in Figure 1, except that these rats were run in two replications, with the first day of deprivation occurring 122 days following exposure for the first replication and 137 days following exposure for the second replication. To control for the possibility that shipping might have produced an aversion or otherwise affected the rats, 8 irradiated rats and 5 control rats were given an injection of physiological saline (0.9%), which would not be expected to produce a CTA, instead of amphetamine or LiCl on the conditioning day.

RESULTS

Amphetamine- and LiCl-Induced CTA Learning

The effects of exposure to 1 GeV/n ^{56}Fe particles which are shown in Figure 2 were evaluated using a two-way analysis of variance (ANOVA). The ANOVA involves calculating the **F** statistic, which gives the observed ratio for the between-group variance and the within-group variance. The probability (p) of obtaining this value of **F** due to the operation of chance factors for the degrees of freedom (determined by the number of comparisons and the number of subjects, given in parentheses) is taken from a table of critical values. It is generally accepted that a p-value less than 0.05 indicates a significant effect of the independent variable. The overall analysis of variance showed that both the main effects for the comparison between amphetamine and LiCl ($F(1,90) = 63.39$, $p < .0001$) and for dose of radiation ($F(4,90) = 8.74$, $p < 0.0001$) were significant. These results indicate that the behavior of the rats given amphetamine was significantly different than the behavior of the rats injected with LiCl, and that the behavior (CTA learning) of the rats varied as a function of the dose of radiation. The dose x drug interaction was also significant ($F(4,90) = 5.89$, $p = .0003$), indicating that the acquisition of a CTA depended upon an interaction of both the drug administered (amphetamine or LiCl) and the dose of ^{56}Fe (0.0 - 2.0 Gy). Because the interaction term of the ANOVA was significant, two additional ANOVAs were run looking at the effects of amphetamine and LiCl separately, followed by multiple comparisons using the Scheffé procedure. The threshold for the disruption of amphetamine-induced CTA learning by exposure to GeV/n ^{56}Fe particles

was 0.8 Gy. Rats exposed to 0.8 Gy of ^{56}Fe particles showed significantly greater test day sucrose intake than the non-irradiated controls (t (14) = 3.54; $p < .05$); whereas the test day intake of rats exposed to 0.5 Gy did not differ significantly from that of the controls (t (17) = 0.24; $p > .05$). A similar disruption of amphetamine-induced CTA learning was observed in rats exposed to 1.0 or 1.5 Gy compared to the control rats (t (20) = 3.12, $p < .05$; t (16) = 2.92, $p < .05$; respectively). There were no significant differences in test day sucrose intake between any of the groups of rats given these three doses of radiation; such that increasing the dose of radiation within this range did not cause a further disruption of amphetamine-induced CTA learning. Increases in radiation dose to a level greater than 1.5 Gy resulted in decreased sucrose intake, such that the rats exposed to 2 Gy showed an amphetamine-induced CTA that did not significantly differ from that observed with the control rats (t (20) = 0.18, $p > .05$).

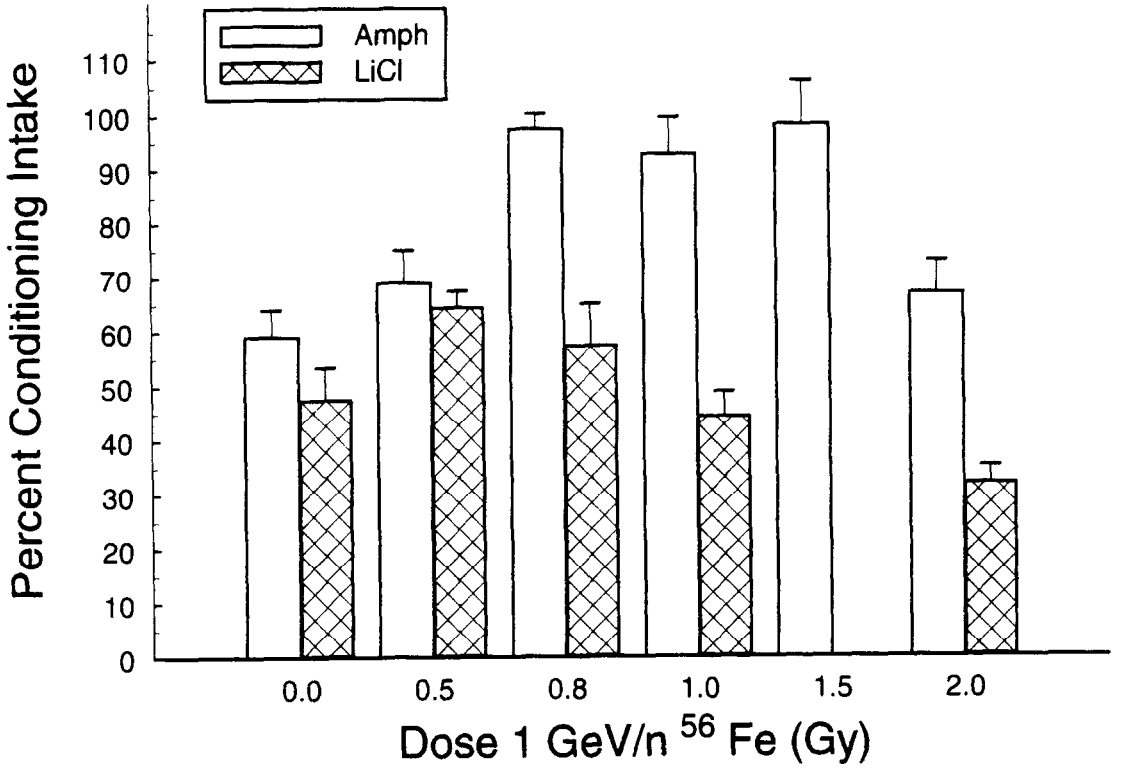

Fig. 2. Effects of exposure to different doses of 1 GeV/n ^{56}Fe particles on amphetamine- (Amph) and lithium chloride- (LiCl) induced taste aversion learning.

In contrast to the results with injection of amphetamine, none of the irradiated rats given injections of LiCl showed a significant disruption of test day sucrose intake compared to the control rats. It is not until a dose of 2 Gy is utilized that there is a non-specific increase in the intensity of the CTA produced by treatment with both LiCl and amphetamine.

For comparison, the effects of exposure to 600 MeV/n ^{56}Fe particles on amphetamine- and LiCl-induced CTA learning (Rabin *et al.*, 1998) are shown in Figure 3. As with the effects of exposure to 1 GeV/n ^{56}Fe particles, there is a significant reduction in the intensity of the amphetamine-induced CTA in rats exposed to either 0.1 or 0.5 Gy. Increasing the dose to 1 Gy, however, resulted in an amphetamine-induced CTA. which did not differ from that of the controls. Exposure to 0.1, 0.5 or 1.0 Gy of ^{56}Fe particles had no effect on the acquisition of the LiCl-induced CTA. However, there is the suggestion that exposing rats to 1 Gy may start to increase the intensity of the CTA produced by injection of both amphetamine and LiCl.

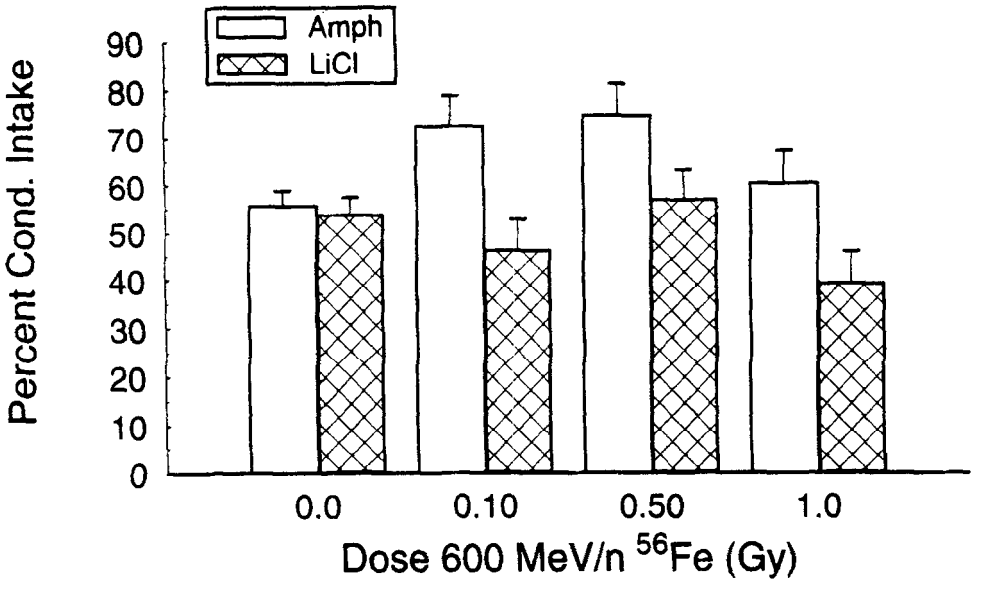

Fig. 3. Effects of exposure to 600 MeV/n ^{56}Fe particles on the acquisition of amphetamine- or LiCl- induced CTA learning. Redrawn from Rabin *et al.* (1998).

Type of Radiation

Figure 4 shows the effects of exposure to fission spectrum neutrons (**A**) and ^{60}Co γ (**B**) (Rabin *et al.*, 1998). Exposing rats to either type of radiation did not selectively disrupt the acquisition of an amphetamine-induced CTA while sparing the acquisition of an LiCl-induced CTA. Rather, there were no significant effects on either amphetamine- or LiCl-induced CTA learning until the rats were exposed to 3 Gy of fission neutrons or 9 Gy of ^{60}Co γ rays. At those doses, both the irradiated and control rats showed significant increases in the avoidance of the sucrose conditioned stimulus following injection of both amphetamine and LiCl. This observation may reflect the increasingly deleterious effects of exposure to higher dose radiation on all forms of behavior, including both conditioned and unconditioned fluid intake

Recovery of Function

Figure 5 summarizes the effects of injection of physiological NaCl (0.9%) on the conditioning day in rats that had been exposed to 1 Gy of ^{56}Fe particles (1 GeV/n) or to sham exposure procedures 4 months prior to behavioral testing. These animals served as controls for the shipping to UMBC and for the delay between exposure and testing. The observation that both the irradiated and control rats given an injection of NaCl on the conditioning day showed increased test day sucrose intake is consistent with previous reports that injection of this dose of NaCl does not produce a CTA (*c.f.*, Hunt and Amit, 1987; Rabin and Hunt, 1986; Riley and Tuck, 1985). As such these results indicate that shipping and the delay interval did not affect CTA learning by themselves.

The comparison of the effects of exposure to 1 Gy of 1 GeV/n ^{56}Fe particles either 3 days or 4 months prior to behavioral testing is shown in Figure 6. For the LiCl-injected rats, there were no significant differences between the irradiated and control animals at either the 3-day (t (15) = 0.195, $p > .05$) or the 4-month (t (15) = 0.014, $p > .05$) intervals. To the contrary, exposing the rats to 1 Gy of ^{56}Fe particles completely disrupted the acquisition of an amphetamine-induced CTA when the conditioning day was three days following exposure. Compared to the control rats, the irradiated rats showed a significantly greater test day sucrose intake (t (21) = 4.22, $p < .05$). In contrast, the rats tested for CTA learning four months following exposure to 1 Gy of ^{56}Fe particles showed an enhanced aversion, ingesting less sucrose, compared to the control subjects (t (19) = -2.24, $p < .05$).

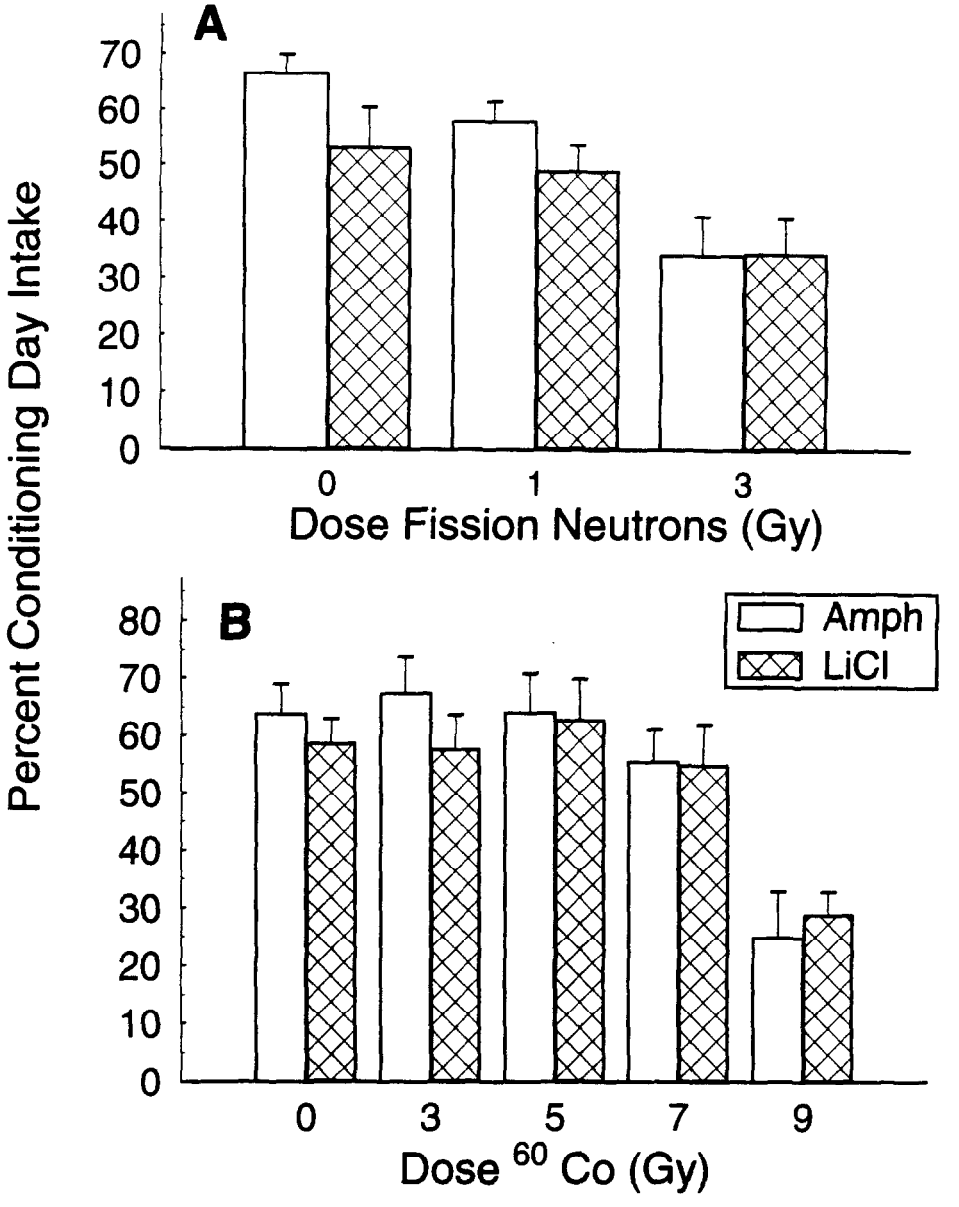

Fig. 4. Effects of exposure to fission spectrum neutrons (**A**) or ^{60}Co γ rays (**B**) on the acquisition of an amphetamine- or LiCl-induced taste aversion. Redrawn from Rabin *et al.* (1998)

DISCUSSION

Pharmacological studies have established that the acquisition of an amphetamine-induced CTA is dependent upon the integrity of the central dopaminergic system (Rabin and Hunt, 1989). Treating rats with the D_2 antagonist haloperidol prevents the acquisition of a dopamine-mediated CTA produced by injection of amphetamine, but has no effect on the CTA produced by injection of LiCl which is not mediated by the central dopaminergic system (Rabin and Hunt, 1986; Smith, 1980). Previous research using heavy particles (600 MeV/n ^{56}Fe) (Rabin *et al.* 1998) has shown that exposing rats to low doses (≈ 0.1 - 1.0 Gy) of these particles mimics the action of haloperidol on dopamine-mediated behavior by blocking the acquisition of an amphetamine-induced CTA, but not an LiCl-induced CTA. The present results with 1 GeV/n ^{56} Fe particles confirm and extend this previous research

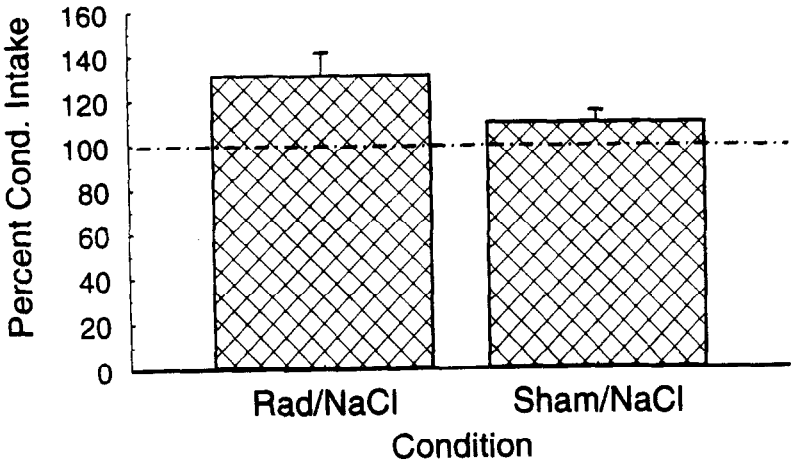

Fig. 5. Effects of injection of physiological saline (NaCl) on sucrose intake of rats tested 4-months following exposure to 1 Gy of 1 GeV/n ^{56}Fe (Rad/NaCl) or non-exposed control rats (Sham/NaCl).

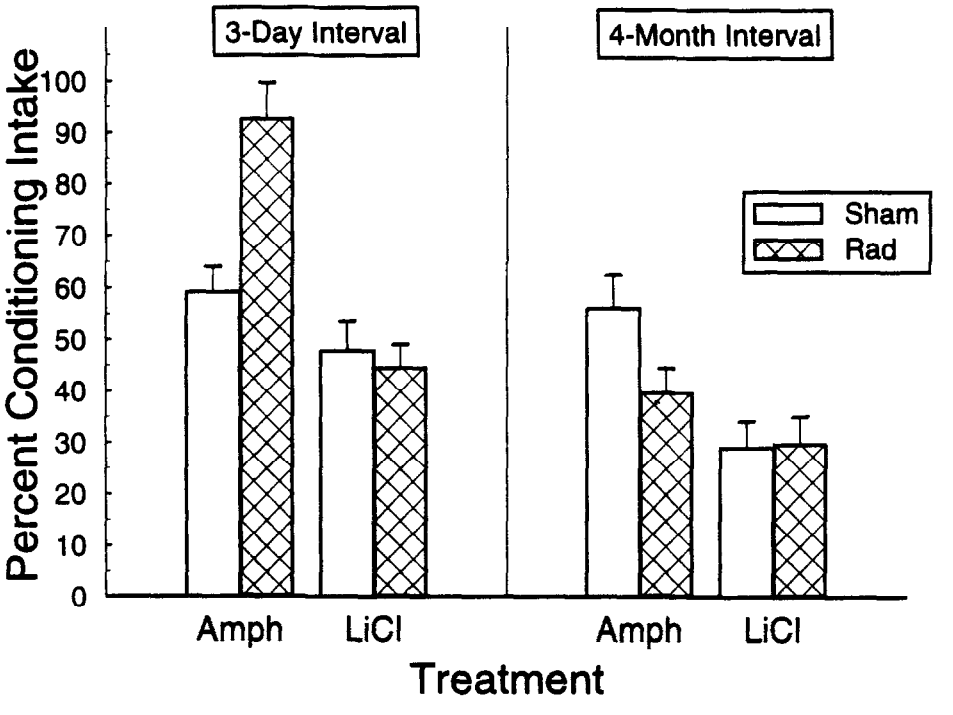

Fig. 6. Effects of exposure to 1 Gy of 1 GeV/n ^{56}Fe particles on the acquisition of amphetamine- or LiCl-induced taste aversions when the conditioning day was 3 days or 4 months following irradiation. The data for the 3-day interval has been redrawn from Figure 2 (1 Gy dose).

Type of Radiation

The results presented above show that the effects of exposure to 1 GeV/n ^{56}Fe particles are similar to the effects of

exposure to 600 MeV/n ^{56}Fe particles on a behavior mediated by the central dopaminergic system. In addition, the results indicate the effects of exposure to heavy particles (^{56}Fe) are qualitatively different from the effects of exposure to other types of radiation (^{60}Co or n ^{0}). A selective effect on the dopamine-mediated amphetamine-induced CTA was observed only following exposure to ^{56}Fe particles and not following exposure to the other types of radiation tested with this behavioral endpoint.

This difference in the relative effectiveness with which these types of radiation produce a selective disruption of the dopamine-mediated CTA is not directly related to LET. This hypothesis is supported by the observations that: (1) despite the fact that the LET of fission spectrum neutrons is ≈ 65 keV/μm, exposure to neutrons was no more effective that exposure to ^{60}Co γ rays with an LET ≈ 0.3 keV/μm in producing selective effects on the central dopaminergic system. (2) increasing the dose of both ^{60}Co and n^0 ultimately caused a general disruption of all behavior, both the dopamine-dependent amphetamine-induced CTA and the dopamine-independent LiCl-induced CTA, probably as the result of a radiation-induced illness. Although the doses of ^{60}Co and fission spectrum neutrons utilized in these experiments were below the doses required to produce CNS radiation syndrome, the highest doses of these types of radiation were at the $LD_{50/30}$ and were in the range needed to produce GI syndrome (Prasad, 1995). The effects of exposure on the GI tract were most likely responsible for the non-selective disruption of both amphetamine- and LiCl-induced CTA learning.

Relationship Between LET and RBE

The LET of the 1 GeV/n ^{56}Fe particles produced at the AGS is ≈ 150 keV/μm and that of the 600 MeV/n ^{56}Fe particles produced at the BEVALAC was ≈ 189 keV/μm. The differences in LET are reflected as: (1) differences in the threshold dose for the alteration of the dopamine-mediated behavior; and (2) the dose at which there is a generalized, non-specific alteration of both dopamine-mediated (amphetamine-induced CTA) and non dopamine-mediated (LiCl-induced CTA) behaviors. In general, the higher the particle LET, the lower the threshold for the disruption of amphetamine-induced CTA learning. Similarly, the effect of LET on the behavioral effectiveness of ^{60}Co and n^0 irradiation, is also seen in terms of the lower dose of fission spectrum neutrons which produces a generalized disruption of all tested behavioral responding. Thus, 3 Gy of n^0 produces a significant alteration in the effects of administration of both amphetamine and LiCl on CTA learning compared to a dose of 9 Gy needed to observe these effects following exposure to ^{60}Co γ rays.

Also, in contrast to the effects observed with other behavioral endpoints, such as radiation-induced CTA learning and radiation-induced emesis (Rabin *et al.*, 1991, 1992, 1998), differences in RBE are not reflected as differences in the dose-response curve. The dopamine-mediated behaviors described in this report are characterized by the absence of a dose-response curve. Once the threshold is reached, further increases in the radiation dose do not produce corresponding increases in the behavioral endpoint. Rather, once the threshold for the response is reached, a maximal behavioral response is obtained.

Recovery of Function

The data presented above indicate that exposure to ^{56}Fe particles produces a permanent change in neural functioning. Initially, when tested 3 days following exposure, this change is reflected as the disruption of a behavior (the amphetamine-induced CTA that is dependent upon the integrity of the central dopaminergic system. When tested 4 months following exposure, there was still evidence of an alteration of neural functioning. However, at this time point, the alteration in neural functioning was shown as a reversal of the initial disruption of amphetamine-induced CTA learning; such that administration of the standard dose of amphetamine produced an enhanced taste aversion.

Although the mechanisms that might be responsible for the enhanced effect of amphetamine must be speculative at the present time, it is possible that the loss or inactivation of dopamine neurons produced by exposure to ^{56}Fe particles causes denervation supersensitivity, an increased sensitivity of the remaining dopamine receptors which compensates for the loss of receptors. It has been reported that one of the negative side effects of maintained administration of the dopamine D_2 antagonist haloperidol for the treatment of schizophrenia is to cause an up-regulation of the dopamine receptors (Aminoff, 1995). As result of the increase in the number of dopamine receptors, small amounts of dopamine come to elicit an enhanced response. Behaviorally, the supersensitivity of the dopamine receptors, either by themselves or because of their interaction with acetylcholine receptors in the striatum, can result in the development of Parkinson-like symptoms and in tardive dyskinesia (Aminoff, 1995; Hollister, 1995; Carvey, 1998). However, the evaluation of

whether or not similar mechanisms are involved in this behavior will require additional experiments specifically designed to determine the effects of exposure to heavy particles on dopamine receptors. These experiments might include studies utilizing immunohistochemical techniques or studies utilizing radioactive labeling of receptors or PET scans.

SUMMARY AND CONCLUSIONS

The key findings of the present report are that: (1) the effects of exposure to ^{56}Fe particles on dopamine-mediated behavior are qualitatively different that the effects of exposure to other types of radiation, including ^{60}Co γ rays and fission spectrum neutrons; (2) there is no dose-response curve following exposure to ^{56}Fe particles for behaviors mediated by the central nervous system - the behavioral effects are characterized by a threshold, such that once the threshold for producing an effect is reached further increases in radiation do not produce a corresponding increase in the behavioral endpoint; and (3) there is a permanent alteration in neural functioning, although this may be reflected as a reversal in the behavioral endpoints under consideration.

Given that exposure to ^{60}Co γ rays, unlike exposure to^{56} Fe particles, does not selectively affect dopamine-mediated behavior, it may not be possible to determine a "quality factor" applicable to exposure to heavy particles for this behavioral endpoint. As such, it may not be possible to establish dose limits based upon quality factors (*e.g.*, Sv) that would be relevant to central nervous system-mediated effects for astronauts on extended missions outside the magnetic shield of the earth.

The doses used in these experiments ranged between 0.1 Gy and 1.0 Gy for 600 MeV/n ^{56}Fe particles and between 0.5 Gy and 2.0 Gy for the 1 GeV/n ^{56}Fe particles. Current estimates are that during a Mars mission, astronauts may be exposed to 0.2 Gy/year from exposure to cosmic rays (*e.g.*, Badhwar *et al.*, 1994). The estimated dose is above the threshold for the behavioral effects observed following exposure to 600 MeV/n ^{56}Fe particles ($\approx$ 0.1 Gy), but is below the threshold following exposure to 1 GeV/n ^{56}Fe particles ($\approx$ 0.8 Gy). However, it must be noted that the doses of radiation in these experiments was delivered using a single acute exposure in contrast to the continuous exposure to lower doses of heavy particles which will be stretched out across the duration of a 3-year mission. As such, it remains to be established whether or not effects similar to those reported here will be produced by the chronic exposure to heavy particles which would characterize the exposure pattern during a Mars mission. On the other hand, the interactive effects of combined exposures to different types and energies of heavy particles and to other types of radiation, such as protons, as well potential interactions with microgravity on behavioral endpoints remain to be established.

Alternate approaches to risk assessment have been proposed by Curtis *et al.* (1998) and by Katz and Cucinotta (1998) and Cucinotta *et al.* (1998). These approaches attempt to calculate the frequency with which a single cell may be hit by a heavy particle. Using this approach, is has been estimated (Curtis *et al.*, 1998), that following exposure to 0.5 Gy each cell could receive two hits. When the effects of delta rays generated by the passage of cosmic rays through biological tissue is also taken into account Cucinotta *et al.* (1998), the number of cells affect by the passage of a heavy particle may be significantly increased. In addition Katz and Cucinotta (1998) note that a heavy particle, as it passes through the brain, has the potential to produce a column of dead cells which may, in turn, indirectly affect the functioning of related cells. Thus the effect of exposure to heavy particles may be do produce "micro lesions" in the brain, the extent of which may be related to particle energy and dose. These approaches place a premium on determining the amount of cell loss attributable to heavy particle exposure, and the relationship of cell loss to central nervous system functioning and behavioral performance. This determination is also complicated by the fact that the amount of tissue loss due to the direct action of heavy particles may interact with tissue loss due to the effects of micro gravity-induced free radical generation (Hollander *et al.*, 1998) and to aging (Joseph *et al.*, 1992. 1993, in press).

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